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SILLS CUMMIS EPSTEIN & GROSS P.C.
ONE RIVERFRONT PLAZA
IP DEPARTMENT
NEWARK, NJ 07102

EXAMINER	
BORGEEST, CHRISTINA M	

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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,087	LAMPING ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-28 and 30-57* is/are pending in the application.

4a) Of the above claim(s) *21,22,25,26 and 30-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-20,23,24,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed 3 August 2007 is acknowledged. Claims 1, 2, 3, 6, 9, 23, 27 and 28 are amended. Claims 7 and 29 are cancelled. Claims 1-6, 8-20, 23-24 and 27-28 are under examination.

Objections/Rejections withdrawn

Oath/Declaration

The objection to the declaration as set forth at p. 3 of the previous Office action mailed 7 March 2007 for improperly claiming foreign priority to PCT DE02/01736 under 35 U.S.C. 119 is withdrawn in response to Applicants' submission of a corrected declaration claiming priority under 35 U.S.C. 120.

Claim Objections

The objection to claims 2 and 3 for reciting non-elected species is withdrawn in response to Applicants' amendment of the claims.

Claim Rejections - 35 USC § 112, first paragraph

The rejection of claims 7 and 29 under 35 U.S.C. 112, first paragraph for scope of enablement as set forth at pages 4-7 of the previous Office action mailed 7 March 2007 is withdrawn in response to Applicants' cancellation of claims 7 and 29.

Claim Rejections - 35 USC § 102

The rejection of claims 7 and 29 under 35 U.S.C. 102(b) as being anticipated by Alberini et al. (WO 01/74298, published 11 October 2001), which is identical to the pre-grant publication, 20030166555, filed 20 September 2002 as set forth at pages 7-11 of the previous Office action mailed 7 March 2007 is withdrawn in response to Applicants' cancellation of claims 7 and 29.

The rejection of claims 7 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Lo et al., US Patent No. 6,277,974, which was issued 21 August 2001 and filed 14 December 1999 as set forth at pages 11-14 of the previous Office action mailed 7 March 2007 is withdrawn in response to Applicants' cancellation of claims 7 and 29.

Objections/Rejections Maintained

Priority

The issues raised at p. 3 of the previous Office action mailed 7 March 2007 were not addressed in Applicants' response, thus the effective filing date remains **6 October 2003**.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-6, 8-20, 23-24 and 27-28 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting Alzheimer's (or other types of dementia indicated in the prior art as being enabled) comprising measuring the VGF peptide having the sequence set forth in SEQ ID NO: 11 (VGFARP-13) in the cerebrospinal fluid (CSF) of patients, wherein lower levels of said VGF peptide relative to controls is indicative of Alzheimer's, wherein said method is carried out in combination with other diagnostic methods for Alzheimer's, does not reasonably provide enablement for the claims as broadly recited as set forth at pages 4-7 of the previous Office action mailed 7 March 2007 is maintained for reasons of record and the following.

First, Applicants' amendment has resolved the first issue of breadth raised by Examiner by limiting the method of detection to Alzheimer's Disease.

Applicants cite case law at p. 15, to which the Examiner takes no issue.

Applicants argue at p. 16, 1st paragraph that the present specification provides adequate teaching and examples to support the claim elements with regard to obtaining a biological sample from a patient, determining the concentration of the peptides in the sample and comparing the concentration of peptides with a control sample to elucidate the difference which indicates Alzheimer's disease or a predisposition thereof (Examples 1-5, respectively).

This argument has been fully considered but is not found persuasive. First, the Examples outlined by Applicants provide enablement for exactly what was found

enabled by the Examiner, namely, the "biological sample" was the CSF and lower levels of VGF peptide relative to controls was found to be indicative of Alzheimer's. In other words, the evidence is not commensurate in scope with the full breadth of the claims. The evidence shows that CSF is the appropriate biological sample and that lower, not higher levels of VGF may be indicative of Alzheimer's. Finally, it is not clear from the teachings in the specification or the literature what the level of protein must be (i.e. how high or low) before a diagnosis can be made, thus the claimed method should be carried out in combination with other diagnostic methods for detecting Alzheimer's.

Applicants argue at p. 16, 1st paragraph that since the processes and steps utilized in accordance with the method of claim 1 are known to those of ordinary skill in the art, the experimentation as set forth in the specification cannot be characterized as undue.

Again the issue is that the evidence is not commensurate in scope with the claims. First, there is no indication in the specification or the literature what the level of protein must be (i.e. how high or low) before a diagnosis can be made, only that there are slightly lower levels of VGF in Alzheimer's patients with respect to controls. The claims encompass diagnosis of methods based on either up- or down-regulation of the VGF peptide, whereas the evidence only shows that there are slightly lower levels of VGF in Alzheimer's patients with respect to controls. The evidence from the specification and the prior art suggests to the person of skill in the art that the higher levels of VGF measured in the CSF might be useful in aiding a diagnosis of schizophrenia and that lower levels of VGF measured in the CSF might be useful in aiding the diagnosis of Alzheimer's or frontotemporal dementia, however, not for the claims as broadly recited. See MPEP 2164.08; questions of enablement are evaluated

against the claimed subject matter, i.e., the focus of the examination inquiry is whether everything within the scope of the claim is enabled. In biotechnology in general, and in diagnosis of dementia and/or neurological disease in particular, there is a relatively incomplete understanding in the field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the art (i.e., VGF may be a biomarker for disease in schizophrenia, Alzheimer's and frontotemporal dementia), and the broad scope of protection sought in the claims (i.e., antemortem diagnosis of Alzheimer's measuring VGF in any body tissue or fluid without a recitation of whether there is an up- or a down-regulation in diseased individuals with respect to controls), a rejection under 35 U.S.C. 112, first paragraph for lack of enablement is appropriate.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 1, 2, 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27 and 28 under 35 U.S.C. 102(b) as being anticipated by Alberini et al. (WO 01/74298, published

11 October 2001), which is identical to the pre-grant publication, 20030166555, filed 20 September 2002 is maintained for reasons of record and the following.

Applicants argue at p. 17, 3rd paragraph that anticipation requires the presence of each and every element of the claimed invention, arranged as in the claim, to which the Examiner takes no issue.

Applicants argue at p. 17, 4th paragraph that Alberini et al. do not anticipate claim 1.

Applicants argue at p. 18, 1st and second paragraphs that Alberini et al. are focused on genes that are up or down regulated in long term memory loss and that they postulate that long term memory consolidation can be modulated by treating an animal with an agent that includes, amongst others, VGF and discloses methods for identifying agents that modulate memory consolidation which include the steps of providing a reaction system for detecting the activity of a product or for detecting the level of expression of a gene and that they do not recite the steps as recited in claim 1.

Applicants argue at p. 19, 3rd paragraph that claim 23 is not anticipated as it incorporates all the limitations of claim 1.

Applicants argue at p. 18, last paragraph to p. 19, 1st paragraph that the teachings Alberini et al. involve the use of a test compound which contacts with the reaction system to determine if there is an alteration in the activity of a gene and that they teach an assessment or measurement method.

These arguments have been fully considered but are not found persuasive for the following reasons.

Alberini et al. (WO 01/74298) teach diagnostic and prognostic assays to determine if a subject is at risk for a disorder characterized deterioration of memory consolidation (i.e., memory disorder; see p. 40, last paragraph; p. 43-45, whole pages) using antibodies to long term memory or LTM proteins, and VGF is defined as one of these proteins (see p. 6, last paragraph to p. 7, 1st paragraph; p. 24, 1st paragraph). One such memory disorder contemplated in their application is Alzheimer's (see p. 7, 3rd paragraph; p. 39, 2nd paragraph). Alberini et al. further teach that "antibodies directed

against wild type or mutant LTM proteins, which are discussed, above, may also be used in disease diagnostics and prognostics. Such diagnostic methods, may be used to detect abnormalities in the level of LTM protein expression," in tissue (see p. 43-45, whole pages). Different types of immunoassays are contemplated, including radioimmunoassay, ELISA and western blot (see p. 43-45, whole pages).

See also p. 41 of Alberini et al, wherein it states:

> Antibodies directed against wild type or mutant LTM proteins, which are discussed, above, may also be used in disease diagnostics and prognostics. **Such diagnostic methods may be used to detect abnormalities in the level of LTM protein expression**, or abnormalities in the structure and/or tissue, cellular, or subcellular location of LTM protein. Structural differences may include, for example, differences in the size, electronegativity, orantigenicity of the mutant LTM protein relative to the normal LTM protein. **Protein from the tissue or cell type to be analyzed may easily be detected or isolated using techniques which are well known to one of skill in the art, including but not limited to western blot analysis**. For a detailed explanation of methods for carrying out western blot analysis, see Sambrook et al, 1989, supra, at Chapter 18 (emphasis added).

VGF, which is defined by Alberini et al. as a LTM protein can be used in disease diagnostics, and 2 pages earlier in the disclosure Alzheimer's is contemplated as one of the diseases comprising such memory consolidation disorders. Furthermore, Alberini et al. state that well known methods for measuring protein levels (such as western blot) can be used to detect "abnormalities in the level of LTM protein expression." Since Alberini et al. teach looking for abnormalities in the level of LTM protein expression, it is reasonable to conclude that they are comparing the levels to a control value, as it is standard medical procedure to determine a range of normal values. It is also reasonable to conclude that since Alberini et al. are performing diagnostic methods, that

they are measuring the LTM proteins in tissue. Claim 1 recites a method for detecting a Alzheimer's Disease in a patient in need thereof comprising the steps of obtaining a biological sample from said patient, determining a concentration of at least one VGF protein or VGFARP peptide in the biological sample, comparing the concentration of the at least one VGF protein or VGFARP peptide in the biological sample to the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample, wherein a difference between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of Alzheimer's disease or a predisposition to Alzheimer's disease. The claims do not recite anything that can be distinguished from the above-referenced passages of Alberini et al.

The rejection of claims 1, 2, 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27 and 28 under 35 U.S.C. 102(b) as being anticipated by Lo et al., US Patent No. 6,277,974, which was issued 21 August 2001 and filed 14 December 1999 as set forth at pages 11-14 of the previous Office action mailed 7 March 2007 is maintained for reasons of record and the following.

Applicants argue at p. 19, last paragraph that Lo et al. (referred to as "the '974 patent" by the Examiner) are focused on the diagnosis and treatment of conditions involving cell death.

Applicants argue at p. 20, 1st paragraph that anticipation requires the presence of each and every element of the claimed invention, arranged as in the claim, to which the Examiner takes no issue.

Applicants argue at p. 20, 2nd and 3rd paragraphs that Lo et al. do not recite each an every element of amended claim 1 and are focused on treatment of stroke, and that no "positive proof connecting cell death with Alzheimer's was provided in Lo nor by the Examiner." Applicants describe the mechanism of Alzheimer's disease pathology at p. 21, to which the Examiner takes no issue. Finally Applicants argue at p. 21, 1st paragraph that the pathology (Applicants presumably mean cell death) differs significantly from the claims in the present application, which are not directed to the administration of protective sequences but rather are focused on providing an indication of the presence of Alzheimer's disease or a predisposition to Alzheimer's disease.

Applicants argue at p. 21, last paragraph that claim 23 is not anticipated as it incorporates all the limitations of claim 1.

These arguments have been fully considered but are not found persuasive for the following reasons. The '974 patent teaches methods of diagnosis of conditions, disorders, or diseases involving cell death, including, but not limited to, neurological disorders such as stroke, using "protective sequences", their products (i.e., proteins), or antibodies that may be used diagnostically, and methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of conditions or disorders involving cell death, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such conditions, disorders, or diseases involving cell death (see column 2, lines 10-45). One of the "protective sequences" taught in the '974 patent is CNI-00724, which has 94% identity to VGF nerve growth factor mRNA (see column 23, Table 11, lines 20-28; column 76, lines 45-60). The '974 patent also contemplates chemical or post-translational modification of the proteins, see for example, column 38, lines 63-67 to column 39, lines 1-4. In addition to stroke, the '974 patent contemplates other diseases associated with cell death, including Alzheimer's (see column 37, lines 11-29). The argument that cell death is not involved in Alzheimer's disease is not persuasive. As early as 1993, Loo et al. found that

apoptosis is induced by β-amyloid in cultured CNS neurons (Proc. Natl. Acad. Sci. USA; 1993; 90: 7951-7955). More recently, it has been reported by Abdul et al. (Journal of Neurochem. 2006; 96: 1322-1335) apoptosis is evident in the brains of Alzheimer's diseased patients and in cultures of neurons exposed to β-amyloid since this protein " impairs mitochondrial redox activity and increases the generation of ROS." Finally, Abdul et al. report that several studies also suggest that β-amyloid-induced oxidative stress lead to apoptotic neuron death that can be inhibited by antioxidants.

Finally, the '974 patent teaches the protective sequences can be used to diagnose, monitor therapy and that various immunoassays can be employed (i.e., antibodies can be used to detect the proteins—see column 58, lines 65-67 to column 59, 60 and 61—entire columns):

> Protective sequence products (i.e. proteins) of the invention, including both wild-type and mutant protective sequence products, conserved variants and polypeptide fragments thereof...may be detected using antibodies which are directed against such gene products. Such antibodies...may thereby be used as diagnostics and prognostics for a condition, disorder, or disease involving cell death. Such methods may be used to detect abnormalities in the level of protective sequence expression or of protective sequence product synthesis, or abnormalities in the structure, temporal expression and/or physical location of protective sequence product. The antibodies and immunoassay methods described herein have, for example, important in vitro applications in assessing the efficacy of treatments for conditions, disorders, or diseases involving cell death...In vitro immunoassays may also be used, for example, to assess the efficacy of cell-based gene therapy for a condition, disorder, or disease involving cell death. Antibodies directed against protective sequence products may be used in vitro to determine, for example, the level of protective sequence expression achieved in cells genetically engineered to produce the protective sequence product. In the case of intracellular protective sequence products, such an assessment is done, preferably, using cell lysates or extracts. Such analysis will allow for a determination of the number of transformed cells necessary to achieve therapeutic efficacy in vivo, as well as optimization of the gene

> replacement protocol...The protein isolation methods employed herein may, for example, be such as those described [in the prior art]. The isolated cells can be derived from cell culture or from a patient...Preferred diagnostic methods for the detection of protective sequence products, conserved variants or peptide fragments thereof, may involve, for example, immunoassays wherein the protective sequence products or conserved variants or peptide fragments are detected by their interaction with an anti-protective sequence product-specific antibody. Immunoassays for protective sequence products, conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells or lysates of cells in the presence of a detectably labeled antibody capable of identifying the protective sequence product, conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art. One of the ways in which the protective sequence product-specific antibody can be detectably labeled is by linking the same to an enzyme, such as for use in an enzyme immunoassay...Detection may be accomplished also using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect protective sequence products through the use of a radioimmunoassay (RIA)...

The claims do not recite anything that can be distinguished from the above-referenced passages of Lo et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claim 6 under 35 U.S.C. 103(a) as being unpatentable over Alberini et al. as applied to claims 1, 2, 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27, and 28 above, and further in view of Bennet et al. (Dis Mon. 1992, 38: 1-64) as set forth at pages 15-16 in the Office action mailed 7 March 2007 is maintained for reasons of record and the following.

Applicants argue at p. 23, 2nd full paragraph that Bennet is dated January 1992 and that reliable diagnostic methods for AD were uncommon at that time and that the instant claims proffer a reliable diagnostic method for indicating the presence of Alzheimer's.

Applicants argue at p. 23, 3rd full paragraph that since claim 6 depends directly from claim 1, it incorporates all the limitations of independent claim 1 and is patentable over Alberini et al. and Bennet for the same reasons asserted with regard to claim 1.

These arguments have been fully considered but are not found persuasive for the following reasons. Applicants criticize Bennet by stating that reliable diagnostic methods for AD were uncommon at that time and state that their claimed method proffers a reliable diagnostic method for indicating the presence of Alzheimer's. Applicants have not overcome the Examiner's assertion that Bennet teach that antemortem diagnosis of Alzheimer's is best achieved through a combination of clinical history, physical and neurologic examination and laboratory evaluation. In spite of the

age of the Bennet reference, a multi-pronged approach to antemortem Alzheimer's disease diagnosis is still the most prudent medical course. Furthermore, the reference highlights the skill of the ordinary artisan, which in this case is a medical doctor. Applicants have not provided any evidence that current antemortem diagnosis is routinely conducted by the person of ordinary skill in the art (POSITA) using a single assay and/or approach. With regard to Applicants argument that claim 6 depends from claim 1, the Examiner has maintained the rejection of claim 1 over Alberini et al. See the comments addressed to Applicants remarks in the rejection under 35 U.S.C. 102(b), which are applicable here).

The rejection of claim 6 under 35 U.S.C. 103(a) as being unpatentable over Lo et al., US Patent No. 6,277,974, as applied to claims 1, 2, 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27 and 28 above, and further in view of Bennet et al. (Dis Mon. 1992, 38: 1-64).

Applicants argue at p. 24, last paragraph that Bennet is dated January 1992 and that the instant claims proffer a reliable diagnostic method for indicating the presence of Alzheimer's.

Applicants argue at p. 25, 1st full paragraph that since claim 6 depends directly from claim 1, it incorporates all the limitations of independent claim 1 and is patentable over Lo et al. (referred to by the Examiner as "the '974 patent" and Bennet for the same reasons asserted with regard to claim 1.

These arguments have been fully considered but are not found persuasive for the following reasons. Applicants appear to level the same criticism against Bennet here as they did above, but they only state that their claimed method proffers a reliable diagnostic method for indicating the presence of Alzheimer's. Applicants have not

overcome the Examiner's assertion that Bennet teach that antemortem diagnosis of Alzheimer's is best achieved through a combination of clinical history, physical and neurologic examination and laboratory evaluation. In spite of the age of the Bennet reference, a multi-pronged approach to antemortem Alzheimer's disease diagnosis is still the most prudent medical course. Furthermore, the reference highlights the skill of the ordinary artisan, which in this case is a medical doctor. Applicants have not provided any evidence that current antemortem diagnosis is routinely conducted by the POSITA using a single assay and/or approach. With regard to Applicants argument that claim 6 depends from claim 1, the Examiner has maintained the rejection of claim 1 over the '974 patent. See the comments addressed to Applicants remarks in the rejection under 35 U.S.C. 102(b), which are applicable here).

The rejection of claims 11, 12, 17, 18 and 19 under 35 U.S.C. 103(a) as being unpatentable over Alberini et al. (WO 01/74298) as applied to claims 1, 2, 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27 and 28 above, and further in view of Chambers et al. (J Pathol. 200; 192: 280-288) is maintained for reasons of record and the following.

Applicants argue at p. 26, 2nd paragraph that since dependent claims 11, 12 and 17-19 remain patentable because the cited additional reference does not supply the elements missing from Alberini et al. with respect to claim 1 and cite that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."

This argument has been fully considered but is not found persuasive. The Examiner did not "pick and choose" from Alberini et al. Alberini et al. contemplate many

different methods, one of which is diagnostic and prognostic assays comprising determining if a subject is at risk for a disorder characterized deterioration of memory consolidation (i.e., memory disorder; see p. 40, last paragraph; p. 43-45, whole pages) using antibodies to long term memory or LTM proteins, and VGF is defined as one of these proteins (see p. 6, last paragraph to p. 7, 1st paragraph; p. 24, 1st paragraph). One such memory disorder contemplated in their application is Alzheimer's (see p. 7, 3rd paragraph; p. 39, 2nd paragraph). Alberini et al. further teach that "antibodies directed against wild type or mutant LTM proteins, which are discussed, above, may also be used in disease diagnostics and prognostics. "Such diagnostic methods, may be used to detect abnormalities in the level of LTM protein expression," in tissue (see p. 43-45, whole pages). Different types of immunoassays are contemplated, including radioimmunoassay, ELISA and western blot (see p. 43-45, whole pages).

See also p. 41 of Alberini et al, wherein it states:

> Antibodies directed against wild type or mutant LTM proteins, which are discussed, above, may also be used in disease diagnostics and prognostics. **Such diagnostic methods may be used to detect abnormalities in the level of LTM protein expression**, or abnormalities in the structure and/or tissue, cellular, or subcellular location of LTM protein. Structural differences may include, for example, differences in the size, electronegativity, orantigenicity of the mutant LTM protein relative to the normal LTM protein. **Protein from the tissue or cell type to be analyzed may easily be detected or isolated using techniques which are well known to one of skill in the art, including but not limited to western blot analysis**. For a detailed explanation of methods for carrying out western blot analysis, see Sambrook et al, 1989, supra, at Chapter 18 (emphasis added).

The Examiner focused on the part of the reference that was drawn to diagnostic methods, which is not improper, since the claims are drawn to diagnostic methods.

Typically patent and WO applications contain numerous embodiments including products, therapeutic and diagnostic methods, to name several.

The rejection of claims 11, 12, 17, 18, 19 under 35 U.S.C. 103(a) as being unpatentable over Lo et al., US Patent No. 6,277,974, as applied to claims 1, 2, 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 20, 23, 24, 27 and 28 above, and further in view of Chambers et al (J Pathol. 200; 192: 280-288) is maintained for reasons of record and the following.

Applicants argue at p. 27, 2nd and 3rd paragraphs that since dependent claims 11, 12 and 17-19 remain patentable because the cited additional reference does not supply the elements missing from Lo et al. with respect to claim 1 and cite that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."

This argument has been fully considered but is not found persuasive. The Examiner did not "pick and choose" from Lo et al. (referred to by the Examiner as the "the '974 patent"). The '974 patent teaches several methods, including a method of diagnosing conditions, disorders, or diseases involving cell death, including, but not limited to, neurological disorders such as stroke, using "protective sequences", their products (i.e., proteins), or antibodies that may be used diagnostically, and methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of conditions or disorders involving cell death, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such conditions, disorders, or diseases involving cell death (see column 2, lines 10-45). One of the "protective sequences" taught in the '974 patent is CNI-00724, which has 94% identity

to VGF nerve growth factor mRNA (see column 23, Table 11, lines 20-28; column 76, lines 45-60). The '974 patent also contemplates chemical or post-translational modification of the proteins, see for example, column 38, lines 63-67 to column 39, lines 1-4. In addition to stroke, the '974 patent contemplates other diseases associated with cell death, including Alzheimer's (see column 37, lines 11-29).

Finally, the '974 patent teaches the protective sequences can be used to diagnose, monitor therapy and that various immunoassays can be employed (i.e., antibodies can be used to detect the proteins—see column 58, lines 65-67 to column 59, 60 and 61—entire columns):

> Protective sequence products (i.e. proteins) of the invention, including both wild-type and mutant protective sequence products, conserved variants and polypeptide fragments thereof...may be detected using antibodies which are directed against such gene products. Such antibodies...may thereby be used as diagnostics and prognostics for a condition, disorder, or disease involving cell death. Such methods may be used to detect abnormalities in the level of protective sequence expression or of protective sequence product synthesis, or abnormalities in the structure, temporal expression and/or physical location of protective sequence product. The antibodies and immunoassay methods described herein have, for example, important in vitro applications in assessing the efficacy of treatments for conditions, disorders, or diseases involving cell death...In vitro immunoassays may also be used, for example, to assess the efficacy of cell-based gene therapy for a condition, disorder, or disease involving cell death. Antibodies directed against protective sequence products may be used in vitro to determine, for example, the level of protective sequence expression achieved in cells genetically engineered to produce the protective sequence product. In the case of intracellular protective sequence products, such an assessment is done, preferably, using cell lysates or extracts. Such analysis will allow for a determination of the number of transformed cells necessary to achieve therapeutic efficacy in vivo, as well as optimization of the gene replacement protocol...The protein isolation methods employed herein may, for example, be such as those described [in the prior art]. The isolated cells can be derived from cell culture or from a patient...Preferred diagnostic methods for the detection of protective sequence products,

> conserved variants or peptide fragments thereof, may involve, for example, immunoassays wherein the protective sequence products or conserved variants or peptide fragments are detected by their interaction with an anti-protective sequence product-specific antibody. Immunoassays for protective sequence products, conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells or lysates of cells in the presence of a detectably labeled antibody capable of identifying the protective sequence product, conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art. One of the ways in which the protective sequence product-specific antibody can be detectably labeled is by linking the same to an enzyme, such as for use in an enzyme immunoassay...Detection may be accomplished also using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect protective sequence products through the use of a radioimmunoassay (RIA).

The Examiner focused on the part of the reference that was drawn to diagnostic methods, which is not improper, since the claims are drawn to diagnostic methods. Typically patent and WO applications contain numerous embodiments including products, therapeutic and diagnostic methods, to name several. Thus the claims do not contribute anything non-obvious over the prior art.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 7:00am - 1:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646